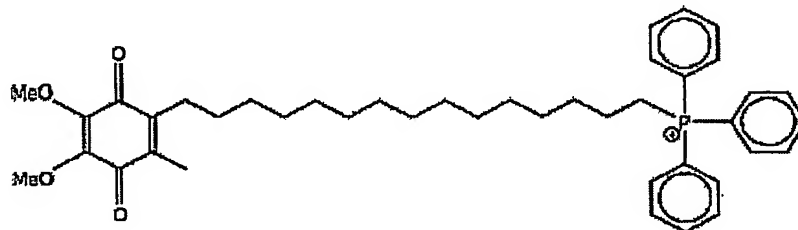


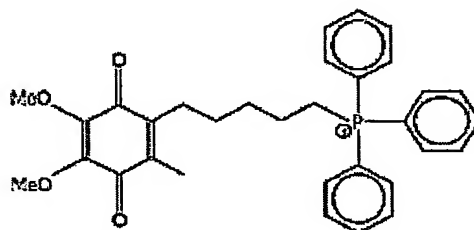
CLAIMS

1. A mitochondrially targeted antioxidant compound having a lipophilic cationic moiety linked by a linking moiety to an antioxidant moiety
5 wherein the nature of the linking moiety, the lipophilic cationic moiety and the antioxidant moiety is such that when targeted to mitochondria the antioxidant moiety is positioned at or proximal to a desired location within said mitochondria.
2. A compound of claim 1 wherein said location is the outer mitochondrial
10 membrane.
3. A compound of claim 1 wherein said location is the intermembrane space of said mitochondria.
4. A compound of claim 1 wherein said location is the inner mitochondrial membrane.
- 15 5. A compound of claim 1 said location is the mitochondrial matrix.
6. A mitochondrially targeted antioxidant compound having a lipophilic cationic moiety linked by a linking moiety to an antioxidant moiety wherein the nature of the linking moiety, the lipophilic cationic moiety and the antioxidant moiety is such that when located in or on or proximal to a
20 mitochondrial membrane the distance from the lipophilic moiety to the antioxidant moiety is between about 5 and about 60 angstroms.
7. A compound of claim 6 wherein the distance from the lipophilic moiety to the antioxidant moiety is between about 10 angstroms and about 50 angstroms.
- 25 8. A compound of claim 7 wherein the distance is between about 20 angstroms and 40 angstroms.
9. A compound of claim 8 wherein the distance is between about 25 angstroms and about 35 angstroms.
10. A compound of claim 6 wherein the linking moiety is a carbon chain
30 having from about 1 to about 30 carbon atoms.

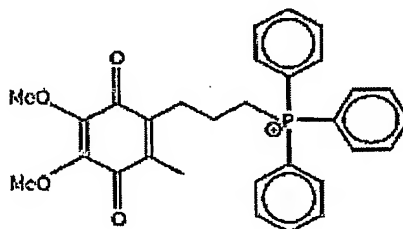
11. A compound of claim 10 wherein the linking moiety is a carbon chain having from about 2 to about 20 carbon atoms.
12. A compound of claim 11 wherein the linking moiety is a carbon chain having from about 2 to about 15 carbon atoms.
- 5 13. A compound according to claim 12 wherein the compound has the formula



14. A compound of claim 12 wherein the linking moiety is a carbon chain having from about 3 to about 10 carbon atoms.
15. A compound of claim 13 wherein the linking moiety is a carbon chain having from about 3 to about 6 carbon atoms.
- 10 16. A compound according to claim 14 wherein the compound has the formula



17. A compound according to claim 14 wherein the compound has the formula



18. A mitochondrially targeted antioxidant compound having a lipophilic cationic moiety linked by a linking moiety to an antioxidant moiety

wherein the antioxidant moiety is capable of interacting with mitochondrial reductants.

19. A compound according to claim 18 wherein the antioxidant moiety is capable of repeated interaction with mitochondrial reductants thereby to achieve a recycling of antioxidant activity.

20. A mitochondrially targeted antioxidant compound having a lipophilic cationic moiety linked by a linking moiety to an antioxidant moiety wherein the antioxidant compound is a better substrate for reduction by components of the mitochondrial respiratory chain than it is a substrate for oxidation by components of the mitochondrial respiratory chain.

21. A method of preparing a mitochondrially targeted antioxidant compound which comprises selecting an antioxidant moiety, selecting a lipophilic cation, selecting a linking moiety capable of linking the antioxidant moiety to the lipophilic cation, wherein the linking moiety, the lipophilic moiety and/or the antioxidant moiety are selected so that when targeted to mitochondria the antioxidant moiety is positioned at or proximal to a desired location within said mitochondria.

22. The method according to claim 21 wherein said location is the outer mitochondrial membrane.

23. The method according to claim 21 wherein said location is the intermembrane space of said mitochondria.

24. The method according to claim 21 wherein said location is the inner mitochondrial membrane.

25. The method according to claim 21 wherein said location is the mitochondrial matrix.

26. A method of positioning the antioxidant moiety of a mitochondrially targeted antioxidant compound having a lipophilic cationic moiety linked by a linking moiety to an antioxidant moiety in a desired location in or on or proximal to a mitochondrial membrane, which involves selecting the linking moiety, the lipophilic moiety and/or the antioxidant moiety so that

when targeted to mitochondria the antioxidant moiety is positioned at or proximal to said desired location within said mitochondria, and contacting said mitochondria with said antioxidant compound.

27. The method according to claim 26 wherein the lipophilic moiety and/or the antioxidant moiety is such that when positioned in or on or proximal to a mitochondrial membrane the distance from the lipophilic moiety to the antioxidant moiety is between about 5 and about 60 angstroms.
28. A method of targeting a desired location of the antioxidant moiety of a mitochondrially targeted antioxidant compound having a lipophilic cationic moiety linked by a linking moiety to an antioxidant moiety, which involves selecting a particular chain length of the linking moiety which will position the antioxidant moiety to the desired location within the mitochondria, and bringing said antioxidant compound into contact with said mitochondria.
29. A method of screening for an amphiphilic antioxidant compound, said method comprising or including administering said compound to a mitochondrial preparation, observing or determining mitochondrial uptake of the compound in the presence of a mitochondrial membrane potential, observing and/or determining release of the compound in the absence of a mitochondrial membrane potential, wherein substantially incomplete release of said compound is indicative of efficacy.
30. The method according to claim 29 wherein uptake and release of said compound is observed and/or determined by methods as herein disclosed.
31. The method according to claim 29 or 30 wherein said compound has uptake and release characteristic of that of Mitoquinone-C10.
32. The method according to claim 29 or 30 wherein said compound has uptake and release so as to have more that characteristic of Figure 3C as opposed to that characteristic of Figure 3A.
33. A method of screening for an amphiphilic antioxidant compound, said method comprising or including administering said compound to a mitochondrial preparation, observing and/or determining mitochondrial

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uptake of the compound in the presence of a mitochondrial membrane potential, observing and/or determining release of the compound in the absence of a mitochondrial membrane potential, wherein substantially complete release of said compound is indicative of efficacy.

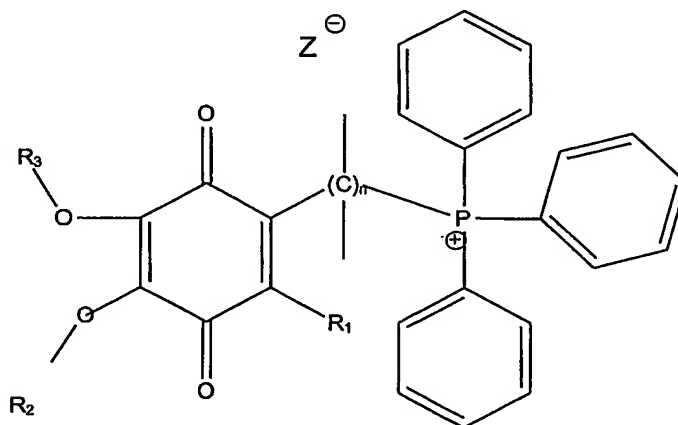
- 5 34. A method of screening for an amphiphilic antioxidant compound, said method comprising or including administering said compound to a mitochondrial preparation, observing and/or determining mitochondrial uptake of the compound in the absence of a mitochondrial membrane potential, wherein at least partial uptake of said compound is indicative of efficacy.
- 10 35. The method according to claim 34 wherein said method comprises one or more additional steps of observing and/or determining uptake of the compound in the presence of a mitochondrial membrane potential, and/or observing and/or determining release of the compound in the absence of a mitochondrial membrane potential, wherein substantially incomplete release of said compound is indicative of efficacy,
- 15 36. The method according to claim 35 wherein uptake and release of said compound is observed and/or determined by methods as herein disclosed.
37. The method according to claim 35 or 36 which said compound has uptake and release characteristic of that of Mitoquinone-C15.
- 20 38. The method according to claim 35 or 36 wherein said compound has uptake and release so as to have more that characteristic of Figure 3D as opposed to that characteristic of Figure 3A.
39. A method of screening for an amphiphilic antioxidant compound, said method comprising or including administering said compound to a mitochondrial preparation, observing and/or determining mitochondrial uptake of the compound in the presence of a mitochondrial membrane potential, observing and/or determining release of the compound in the absence of a mitochondrial membrane potential, wherein complete release of said compound is indicative of efficacy.
- 25 30

40. A method of screening for an amphiphilic antioxidant compound, said method comprising or including administering said compound to a mitochondrial preparation, observing and/or determining mitochondrial uptake of the compound in the absence of a mitochondrial membrane potential, wherein at substantially no uptake of said compound is indicative of efficacy.
41. The method according to claim 40 wherein said method comprises one or more additional steps of observing and/or determining uptake of the compound in the presence of a mitochondrial membrane potential, and/or observing and/or determining release of the compound in the absence of a mitochondrial membrane potential, wherein substantially complete release of said compound is indicative of efficacy.
42. The method according to claim 41 wherein uptake and release of said compound is observed and/or determined by methods as herein disclosed.
43. The method according to claim 41 or 42 wherein said compound has uptake and release characteristic of that of Mi toquinone-C3.
44. The method according to claim 41 or 42 wherein said compound has uptake and release so as to have more that characteristic of Figure 3A as opposed to that characteristic of Figure 3D.
45. A method of reducing oxidative stress in a cell which comprises positioning in or on the outer mitochondrial membrane and/or in the intermembrane space and/or in or on the inner mitochondrial membrane and/or in the matrix an antioxidant moiety of a compound comprising a lipophilic cationic moiety linked to said antioxidant moiety.
46. A method of therapy or prophylaxis of a patient who would benefit from reduced oxidative stress which comprises or includes the step of administering to said patient a mitochondrially targeted antioxidant compound comprising a lipophilic cationic moiety linked by a linking moiety to an antioxidant moiety thereby to position in or on the outer mitochondrial membrane and/or in the intermembrane space and/or in or on

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the inner mitochondrial membrane and/or in the matrix said antioxidant moiety of said compound.

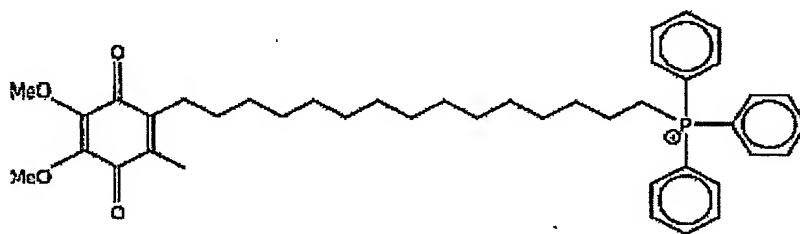
47. A mitochondrially targeted antioxidant compound which comprises a lipophilic cation linked by a linking moiety to an antioxidant moiety, wherein the compound is crystalline or solid, and/or the compound has a partition coefficient (octanol:water) less than about 20, and the compound is a salt form in which the anion is non nucleophilic or exhibits no reactivity against the antioxidant moiety, the linking moiety, or the cationic moiety, and/or the compound is in a salt form where the salt is acceptable for pharmaceutical preparation.
48. A compound according to claim 47 wherein the lipophilic cation is the triphenylphosphonium cation.
49. A compound according to claim 47 or 48 wherein the acceptable salt form is that of the methanesulfonate.
50. A compound according to any of claims 47 to 49 wherein the antioxidant moiety is a quinone or a quinol.
51. A dosage unit suitable for oral administration comprising as an active ingredient a compound according to any of claims 1 to 20, the compound being of or being formulated as a crystalline form and/or non-liquid form.
52. A dosage unit according to claim 51 wherein said compound is a mitochondrially targeted antioxidant compound of the formula I



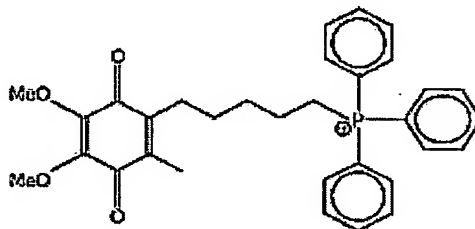
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or its quinol form, wherein R_1 , R_2 , and R_3 , which can be the same or different, are selected from C_1 to C_5 alkyl (optionally substituted) moieties or H, and wherein n is an integer from about 2 to about 20, and wherein Z is an anion, and wherein the compound is crystalline or solid, and/or the compound has a partition coefficient (octanol:water) less than about 20, and the compound is a salt form in which the anion is non nucleophilic or exhibits no reactivity against the antioxidant moiety, the linking moiety, or the cationic moiety, and/or the compound is in a salt form where the salt is acceptable for pharmaceutical preparation.

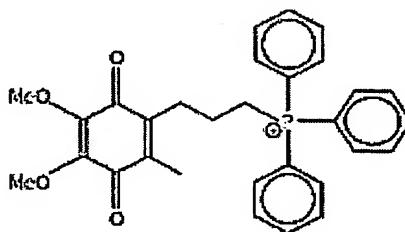
53. A dosage unit according to claim 51 wherein the compound has the formula



54. A dosage unit according to claim 51 wherein the compound has the formula

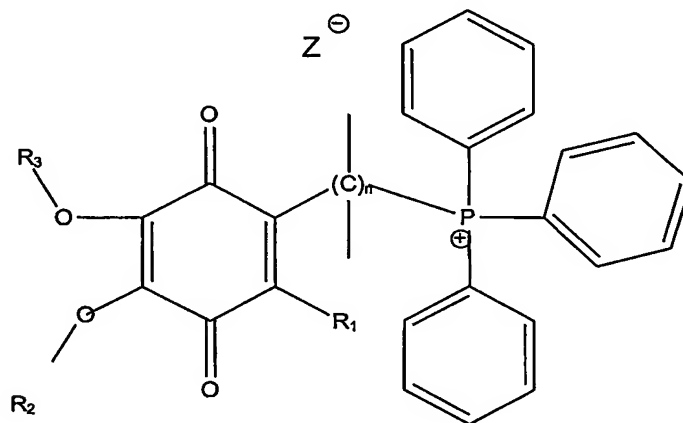


55. A dosage unit according to claim 51 wherein the compound has the formula



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56. A dosage unit suitable for oral administration comprising as an active ingredient a compound according to any of claims 47 to 50, the compound being of or being formulated as a crystalline form and/or non-liquid form.
57. A pharmaceutical composition suitable for treatment of a patient who would benefit from reduced oxidative stress or reduced symptoms of ageing which comprises or includes an effective amount of a mitochondrially targeted antioxidant compound according to any of claims 1 to 20 in combination with one or more pharmaceutically acceptable carriers, excipients or diluents.
58. A composition according to claim 57 wherein said compound is a mitochondrially targeted antioxidant compound of the formula I



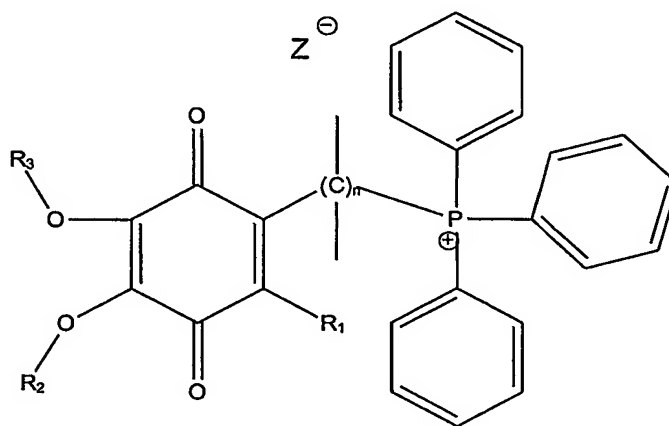
or its quinol form, wherein R₁, R₂, and R₃, which can be the same or different, are selected from C₁ to C₅ alkyl (optionally substituted) moieties or H, and wherein n is an integer from about 2 to about 20, and wherein Z is an anion, and wherein the compound is crystalline or solid, and/or the compound has a partition coefficient (octanol:water) less than about 20, and the compound is a salt form in which the anion is non nucleophilic or exhibits no reactivity against the antioxidant moiety, the linking moiety, or the cationic moiety, and/or the compound is in a salt form where the salt is acceptable for pharmaceutical preparation.

59. A pharmaceutical composition suitable for treatment of a patient who would benefit from reduced oxidative stress or reduced symptoms of ageing which comprises or includes an effective amount of a mitochondrially targeted antioxidant compound according to any of claims 47 to 50 in combination with one or more pharmaceutically acceptable carriers, excipients or diluents.
60. A method of reducing oxidative stress in a cell which comprises the step of contacting said cell with a mitochondrially targeted antioxidant compound according to any of claims 1 to 20.
61. A method of reducing oxidative stress in a cell which comprises the step of contacting said cell with a mitochondrially targeted antioxidant compound according to any of claims 47 to 50.
62. A method of therapy or prophylaxis of a patient who would benefit from reduced oxidative stress or reduced symptoms of aging which comprises or includes the step of administering to said patient a mitochondrially targeted antioxidant compound according to any of claims 1 to 20.
63. A method of therapy or prophylaxis of a patient who would benefit from reduced oxidative stress or reduced symptoms of aging which comprises or includes the step of administering to said patient a mitochondrially targeted antioxidant compound according to any of claims 47 to 50.
64. The use of a mitochondrially targeted antioxidant compound comprising a lipophilic cation linked by a linking moiety to an antioxidant moiety in the preparation or manufacture of a medicament, dosage unit, or pharmaceutical composition effective for use in the reduction of oxidative stress or the reduction of symptoms of aging in a patient, wherein the compound is crystalline or solid, and/or the compound has a partition coefficient (octanol:water) less than about 20, and the compound is a salt form in which the anion is non nucleophilic or exhibits no reactivity against the antioxidant moiety, the linking moiety, or the cationic moiety, and/or

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the compound is in a salt form where the salt is acceptable for pharmaceutical preparation.

65. The use of a mitochondrially targeted antioxidant compound according to any of claims 1 to 20 in the preparation or manufacture of a medicament, dosage unit, or pharmaceutical composition effective for use in the reduction of oxidative stress or the reduction of symptoms of aging in a patient
66. The use of a mitochondrially targeted antioxidant compound according to any of claims 47 to 50 in the preparation or manufacture of a medicament, dosage unit, or pharmaceutical composition effective for use in the reduction of oxidative stress or the reduction of symptoms of aging in a patient
67. A method of synthesis of a compound of the formula I



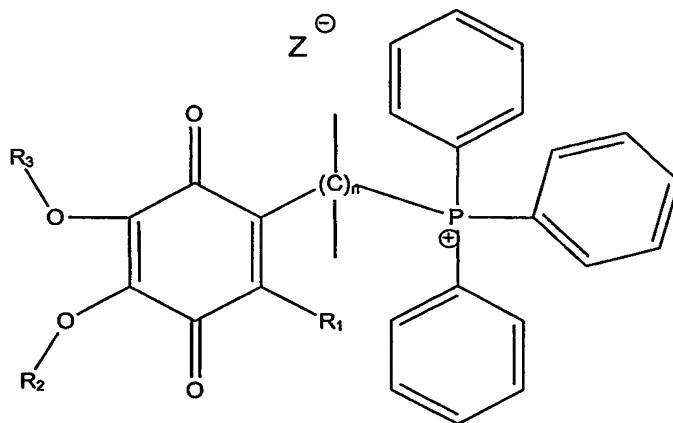
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(and/or its quinone form) wherein R₁, R₂, and R₃, which can be the same or different, are selected from C₁ to C₅ alkyl (optionally substituted) moieties, and wherein n is an integer from about 2 to about 20, and wherein Z is an anion, and the compound is a salt form in which the anion is non nucleophilic or exhibits no reactivity against the antioxidant moiety, the linking moiety, or the cationic moiety, and/or the compound

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is in a salt form where the salt is acceptable for pharmaceutical preparation.

68. A method according to claim 67 wherein each C of the (C)_n bridge is saturated.
- 5 69. A method according to claim 67 or 68 wherein the compound is crystalline or solid.
70. A method according to any of claims 67 or 69 wherein the compound has a partition coefficient (octanol:water) less than about 20.
71. A method according to any of claims 67 to 70 wherein the formation of the
10 compound from triphenylphosphonium does not involve reaction solvent.
72. A method of synthesis of a compound of the formula I

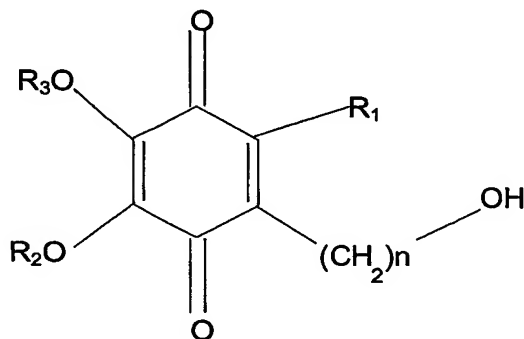


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- (and/or its quinone form) wherein R₁, R₂, and R₃, which can be the same
15 or different, are selected from C₁ to C₅ alkyl (optionally substituted) moieties, and wherein n is an integer from about 2 to about 20, and wherein each C of the (C)_n bridge is saturated, and wherein Z is an anion, and the compound is a salt form in which the anion is non nucleophilic or exhibits no reactivity against the antioxidant moiety, the linking moiety,
20 or the cationic moiety, and/or the compound is in a salt form where the

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salt is acceptable for pharmaceutical preparation which comprises or includes the reaction of a compound of the formula IV



IV

(and/or its quinol form) in the presence of Ph_3PHX and Ph_3P , where X is a halogen atom.

5

73. A method according to claim 72 wherein the halogen is bromine, iodine or chlorine.

74. A method according to claim 73 wherein the halogen is bromine.

75. A method according to any of claims 72 to 74 wherein n is from 2 to about 5.

10

76. A method according to claim 75 wherein n is 3.

77. A method according to any of claims 72 to 76 wherein the reaction is maintained as a temperature below which significant amounts of R_2PPh_3 , or R_3PPh_3 , are not formed by ether cleavage.

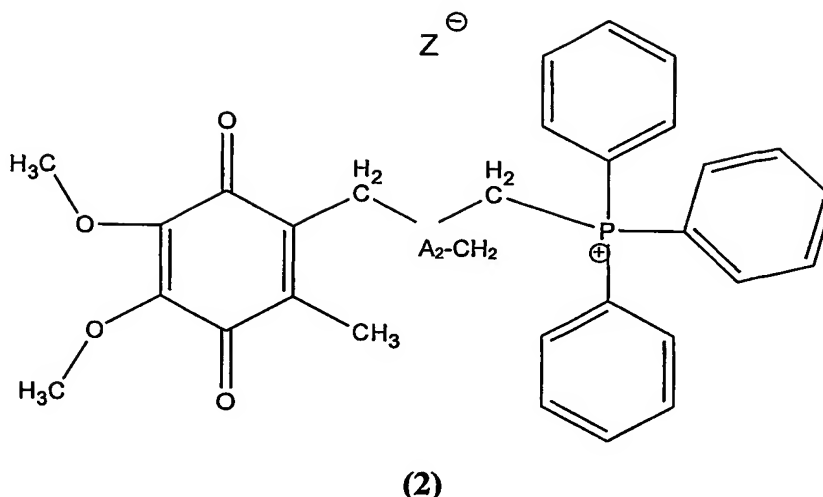
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78. A method according to claim 77 wherein the reaction is kept below 80°C .

79. A method according to any of claims 72 to 78 wherein the formation of the compound from triphenylphosphonium does not involve reaction solvent.

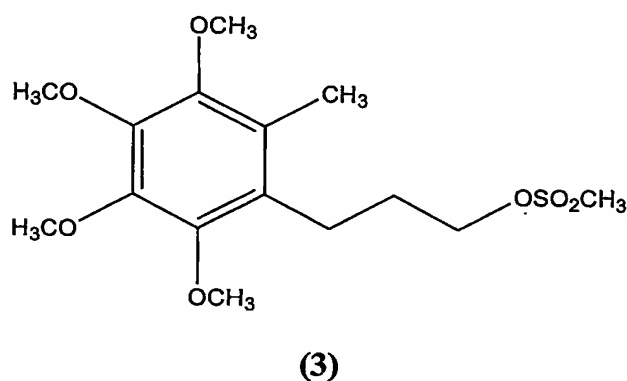
80. A method of synthesis of a compound with a moiety or the moiety of the formula (2)

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(and/or its quinol form), wherein Z is an anion, which comprises or includes the reaction of a compound of the formula (3)

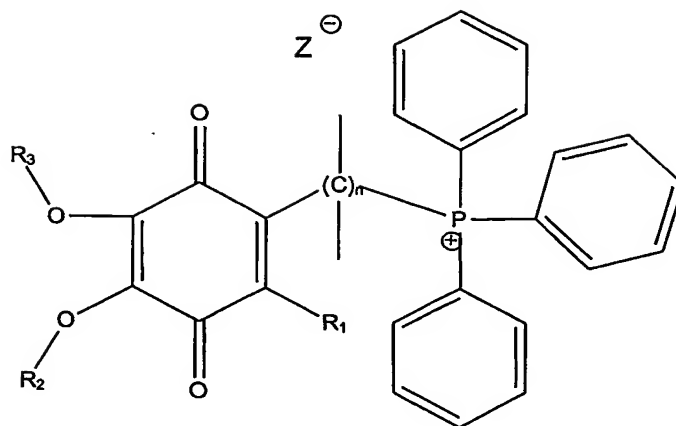
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in the presence of Ph₃P and X, where X comprises or includes a halogen atom.

- 10 81. A method according to claim 80 wherein the halogen is bromine, iodine or chlorine.
82. A method according to claim 81 wherein the halogen is bromine.
83. A method according to any of claims 80 to 82 wherein the formation of the compound from triphenylphosphonium does not involve reaction solvent.
- 15 84. A method of synthesis of a compound of the formula I

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I

(and/or its quinone form) wherein R_1 , R_2 , and R_3 , which can be the same or different, are selected from C_1 to C_5 alkyl (optionally substituted) moieties, and wherein n is an integer from about 2 to about 15, and wherein each C of the $(C)_n$ bridge is saturated, said method substantially as herein described.

85. A method according to claim 84 wherein the method is reliant upon the method depicted in Scheme 1.

10 86. A method according to claim 85 wherein the method is reliant upon the method depicted in Scheme 1 herein in conjunction with that depicted in Scheme 3 herein.

87. A method according to any of claims 84 to 86 wherein the formation of the compound from triphenylphosphonium does not involve reaction solvent.